amendments and the following remarks.

In the Office Action dated January 14, 2003, the specification as originally filed is objected to for minor informalities. Claims 1-27 are rejected under 35 USC §112, first paragraph based on written description. Claims 1-27 are rejected under 35 USC §112, second paragraph as being indefinite. Claims 1-27 are rejected under 35 USC §103(a) as being unpatentable over US Patent No. 5,478,571 to Gala et al (hereinafter "GALA) in view of US Patent No. 5,840,329 to Bai (hereinafter "BAI").

Applicants acknowledge safe receipt of the Notice of References Cited (PTO-892).

In response to these objections and rejections, Applicants have amended the specification, claims 1, 3, 8, 9, and the first claim 21. Claim 11 and the second claim 21 have been cancelled. Applicants respectfully submit that no new matter has been introduced.

Applicant respectfully submits that the amendments have overcome the objections and rejections for the following reasons:

Specification Objection

The specification as originally filed is objected to because of grammatical errors; unclear valence of Ca^{++} on page 6; unclear diagram on page 10; unclear method of extraction and unclear comparison of DZP® to others in Table 3; and trademark uses without generic terminology.

In response to the objections, Applicants have amended the specification to correct grammatical errors.

With regard to the objection regarding the valence of Ca^{++}, Applicants have amended the specification to remove Ca^{++} as one of A^{+}.

With regard to the diagram on page 10, line 17, Applicants have amended the diagram to show a chemical reaction illustrating how a starch- or cellulose-based excipient reacts with a water-absorbing radical (i.e., $-CH_2COONa$) to form the methoxy-acetate sodium linkage (with the key groups in bold fonts).

With regard to page 12, lines 1-8, Applicants have amended the text to correct a minor spelling mistake, i.e., changing "Yung-Zip's DZP®" (as showing in lines 1 and 2, page 12) to -- Yung-Zip DZF® --. This correction is supported by the evidence as shown in Table 3, which indicates that DSF® has a methanol concentration of 900 ppm (i.e., <3000 ppm), which is within the scope of the present claimed invention. No new matter has been introduced. The extraction method for DSF® has been described in Example 1, although extraction methods as shown in Examples 2-4 produce similar results.

Claim Objection

The Examiner objects to Applicants' inclusion of two claim 21's and recommends that the first claim 21 be converted to claim 27. However, after further consideration, Applicants decide to keep the first claim 21 and cancel the second claim 21 (by incorporating the claim limitations from the second claim 21 to the first claim 1).

Claim Rejections under 35 U.S.C. § 112, First Paragraph

Claims 1-27 are rejected under 35 USC §112, first paragraph based on inconformity with written description. The Examiner opines that "[t]he specification disclosure does not

sufficiently teach any excipient which exhibits the necessary properties commiserate with the scope of the claims."

Applicants respectfully submit that the rejections were due primarily to Applicants' inadvertent mistake by mis-spelling the product of the present invention as DZP®, while the correct spelling should be DZF®, as indicated in Table 3 to have a methanol amount of 900 ppm, which is far less than 3000 ppm as described in the claim. In this regard, Applicants have amended the specification on page 12 to correct such a mistake.

With the amendment and the above clarification, Applicants respectfully submit that there should be no question that Applicants had possessed the claimed invention (i.e., having an excipient which contains less than 3000 ppm of residual solvent) at the time the invention was filed.

Claim Rejections under 35 U.S.C. § 112, Second Paragraph

Claims 1-27 are rejected under 35 USC §112, second paragraph as being indefinite. The Examiner alleges that "the term 'water absorbing property' renders the claims in which it appears indefinite."

In response to the rejections, Applicants have amended claim 1 to read "wherein said excipient possesses water-absorbing property which is characterized by the presence of a methoxy alkylcarboxyl ($-CH_2-O-RCOO^-A^+$) group in said excipient; wherein R is a lower alkyl group having 1-4 carbon atoms; and wherein A^+ is Na^+ or K^+." The amendment is firmly supported by the specification on, for example, page 10, lines 4 to the end and page 11, lines 1-18; as well as the original claim 11. No new matter has been added. In light of the amendment

of claim 1, claims 8-9 have been changed accordingly and claim 11 has been cancelled. The possession of the water absorbing property is important because it allows the residual solvent in the excipient to be replaced with water so as to reduce the amount of the residual solvent in the excipient.

There are in fact two types of excipients possessing water-absorbing property described in the present claimed invention. The first type of excipients (as shown in new claims 27-28), without modification, already possesses good water absorbing property within the excipient. The best example of this type of excipient is Starch 1500 from corn starch, which is illustrated in Examples 13-15.

The second type of excipients (as shown in claims 1-26) does not automatically possess a water-absorbing property. Instead, a water absorbing radical, -R-COO^-A^+, must be conjugated to a free carbinol group (-CH_2OH) in the excipient to form a methoxy alkylcarboxyl group (-CH_2 R-COO^-A^+) in order to provide such a water-absorbing property to the excipient. This type of excipient and its water absorbing property modification are best described on page 10, lines 4 to the end of the page, including the amended diagram.

As to the Examiner's rejections regarding the valence of Ca^{++}, Applicants have amended claims 9 and 21 to remove Ca^{++} from the claims.

Claim Rejections under 35 U.S.C. § 103(a)

Claims 1-27 are rejected under 35 USC §103(a) as being unpatentable over US Patent No. 5,478,571 to Gala et al (hereinafter as "GALA") in view of US Patent No. 5,840,329 to Bai (hereinafter as "BAI"). The rejections are respectfully traversed.

To establish a *prima facie* case of obviousness under 35 U.S.C. §103(a), the prior art reference must teach or suggest all the claim limitations. See MPEP §706.02 (j), citing *In re Vaeck*, 947 F.2d 488, 20 USP Q2d 1438 (Fed. Cir. 1991).

The present claimed invention claims a low-residual-solvent excipient (See claims 1-12, and 27-28). The present claimed invention also claims a method for making such low-residual-solvent excipient (See claims 13-26).

As described in claim 1, the present claimed invention contains the following claim limitations:

(1) A low-residual-solvent excipient;

(2) with less than 3000 ppm of solvent in the low-residual-solvent excipient; and

(3) possessing a water-absorbing property which is characterized by the presence of a methoxy alkylcarboxyl group ($-CH_2-O-RCOO^-A^+$) in the excipient.

Also, the excipient claimed in the present invention is not limited to be used in pharmaceuticals. It can be broadly used in other industries, such as fish foods, plant growth regulators, pesticides and herbicides, as indicated in claim 12.

GALA discloses a process for the preparation of pharmaceutical compositions involving the stabilization of the active drug(s) through the reduction of residual alcohol present in a drug/carrier blend. (See Abstract of GALA). As cited by the Examiner, GALA discloses an invention, where:

> "water insoluble drugs are uniformly dispersed within an inert carrier matrix by solubilization in an organic solvent that is then mixed with the carrier excipients and dried. All of the solvent is removed without adverse affects to the drug in questions. The addition of a small amount of water, approximately 2.0% when the solvent is reduced to 80% or below of its original volume in the drug carrier mixture permits the release of the

final 0.3-1.0% of the solvent without destabilizing the drug of interest." (emphasis added). (See Gala et al. at column 1, lines 24-30).

Thus, it is clear based on the reading of the above disclosure that GALA does not deal with reducing residual solvent in an excipient, rather, it deals with removing the solvent from a drug mixture after the drug has been dissolved in a solvent such as alcohol. Needless to say that GALA does not disclose that the excipient it used contains less than 3000 ppm of solvent and possess a water absorbing property which is characterized by the presence of the methoxy alkylcarboxyl group in the excipient.

BAI teaches a pulsatile drug delivery system containing a plurality of particles capable of delivering drug in any desired patterns. Colum 8, lines 12-39 of BAI, as cited by the Examiner, discloses a group of swelling agents and inert pharmaceutical excipients. However, unlike what is said by the Examiner, nowhere in this excerpt can "water absorbing property" of carboxymethylcellulose, sodium starch glycolate, and polysaccharides and/or an excipient with low-residual-solvent of less than 3000 ppm be found. In fact, contrary to what is said by the Examiner, Applicants have demonstrated in the present invention that excipients such as carboxymethylcellose (Examples 9-12), sodium starch glycolate (Examples 1-8), and chitosan (Example 16-19) do not possess "water absorbing property." Rather, they aquire such a water absorbing property by chemical modification of the excipient, i.e., by reacting a water-absorbing radical with the carbinol group of the excipient, so as to add the water absorbing activity to the excipients. Thus, if "BAI teaches that carboxymethylcellulose and sodium starch glycolate, polysaccharides with water-absorbing properties, are known as inert pharmaceutical excipients," certainly it must be teaching away from what is claimed by Applicants.

Since there is neither teachings nor suggestions that the excipients used by GALA and BAI contain less than 3000 rpm of residual solvent and possess the water absorbing property, the combined teachings of GALA and BAI do not render the claimed invention obvious.

In sum, the Examiner fails to establish a *prima facie* case of obviousness because the combined prior art teachings do not provide all of the claim limitations in Applicants' claimed invention. Therefore, the present invention as set forth in amended claims 1-27 is patently distinct from GALA in view of BAI. Applicants respectfully request that the Examiner withdraw the rejections.

In view of the foregoing, the objections and rejections have been overcome and the claims are in condition for allowance, early notice of which is requested. Should the application not be passed for issuance, the examiner is requested to contact the applicant's attorney to resolve the problem.

Attached hereto is a marked-up version of the changes made to the specification and claim by the current amendment. The attached page is captioned **"VERSION WITH MARKINGS TO SHOW CHANGES MADE."**

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE SPECIFICATION:

The paragraph starting at page 1, line 5 has been rewritten as follows:

-- The present invention relates to excipients, particularly disintegrants, that contain low residual solvent (< 3000 ppm). The excipients are preferably polysaccharide products, which include, but are not limited to, starch, amylose, amylopectin, gelatin, starch 1500, sodium starch glycolate, cellulose, microcrystalline cellulose, hydroxypropylcellulose (HPC), carboxymethyl-cellulose (CMC), croscarmellose, hydroxypropylmethylcellulose (HPMC), and chitosan. The most favorable excipient is sodium starch glycolate. The low-residual-solvent excipient is further characterized by its water absorbing property by adding a water-absorbing radical, such as a ($-RCOO^-A^+$) (wherein A^+ is Na^+, or K^+ ~~or Ca^{++}~~; wherein R is a lower alkyl group having 1-4 carbon atoms), to the carbinol groups ($-CH_2OH$) of the excipients to form a methoxy alkylcarboxyl ($-CH_2-O-RCOO^-A^+$) group in ~~linkage to~~ the excipient so as to improve the water absorbing property of the excipients which facilitates the replacement of residual solvent with water. The present invention also relates to a method for reducing residual solvent in excipients. The method includes removing residual solvent from the excipients by way of adding a solvent/water solution containing: (1) about 75-95% (v/v) isopropanol and about 5-25% water (v/v); (2) about 65-95% acetone and about 5-35% water; and (3) about 60-85% methanol and about 15-40% water.--

The paragraph starting at page 2, line 7 been rewritten as follows:

-- The simplest and most economical procedures for the manufacturing of granules and tablets are the direct grinding, granulation, and compression of all the ingredients so that the ingredients are distributed homogeneously. Usually, in addition to one or more active ingredients, at least one pharmaceutical excipient, such as a diluent, a filler, a binder, a disintegrant, a lubricant, etc., is required. An excipient is an inert and non-toxic substance added to the granules or tablets to confer a suitable consistency or form to the drug(s). --

The paragraph starting at page 3, line 19 has been rewritten as follows:

The paragraph starting at page 6, line 18 has been rewritten as follows:

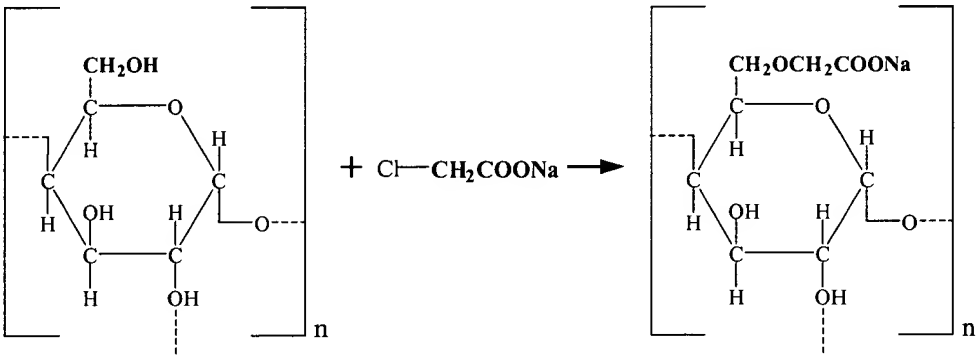
-- The water absorbing property of the low-residual-solvent excipients is obtained by linking a water absorbing radical, such as a ($-RCOO^-A^+$) (wherein A^+ is Na^+, or K^+ ~~or Ca^{++}~~; wherein R is a lower alkyl group having 1-4 carbon atoms), to the carbinol groups ($-CH_2OH$) of the excipients to form a methoxy alkylcarboxyl ($-CH_2-O-RCOO^-A^+$) group ~~linkage of~~ in the excipients. Hereinafter, R is referred to as lower alkyl group with 1-4 carbon atoms and A^+ is referred to as Na^+, or K^+ ~~or Ca^{++}~~. Preferably, R is a straight chain lower alkyl group. The most preferred water absorbing radical is an acetate sodium radical ($-CH_2COO^-Na^+$).--

The paragraph starting at page 9, line 10 has been rewritten as follows:

-- The classification data shown in Table 2 indicates that methanol is classified as class 2 solvent which is more biohazard than ethanol ~~than ethanol~~, a class 3 solvent. That is also the reason why ethanol has a tolerable level of (< 5000 ppm), which is higher than that of methanol

(< 3000 ppm). Thus, the tolerable residual concentration for ethanol is higher than that of methanol.--

The diagram on page 10 has been replaced with the following amended diagram:



The paragraph starting at page 11, line 19 has been rewritten as follows:

-- The significance of using the solvent extraction technique in the present invention can be illustrated by comparing the residual solvent concentration in the commercially available excipient, sodium starch glycolate (a well known binder/disintegrant) with Yung Zip's DZF~~P~~®, which uses the present residue extraction method (Table 3). Yung Zip's DZF~~P~~® is still at the research and development stage and is not currently commercially available.

Table 3. Levels of Residual Solvents in Market Products of Sodium Starch Glycolate --

IN THE CLAIMS:

Claim 1 has been amended as follows:

1. (Amended) 1. (Amended) A low-residual-solvent excipient which has residual solvent of less than 3000 ppm;

wherein said excipient possesses ~~comprises~~ water absorbing property which is characterized by the presence of a methoxy alkylcarboxyl ($-CH_2-O-RCOO^-A^+$) group in said excipient;

wherein R is a lower alkyl group having 1-4 carbon atoms; and

wherein A^+ is Na^+ or K^+.

Claim 3 has been amended as follows:

3. (Amended) The low-residual-solvent excipient according to claim 2~~1~~, wherein said polysaccharide based material is one selected from the group consisting of starch based material, cellulose based material, chitin based material, sugar, Arabic gum, and Guar gum.

Claim 4 has been amended as follows:

4. (Once Amended) The low-residual-solvent excipient according to claim 3, wherein said starch based material is one selected from the group consisting of starch, amylose, amylopectin, gelatin, ~~starch 1500,~~ and sodium starch glycolate.

Claim 8 has been amended as follows:

8. (Amended) The low-residual-solvent excipient according to claim 2, ~~urther comprising~~ wherein said methoxy alkylcarboxyl ($-CH_2-O-RCOO^-A^+$) group of said excipient is obtained by reacting a carbinol group ($-CH_2OH$) of said excipient with a water absorbing radical.

Claim 9 has been amended as follows:

9. (Amended) The low-residual-solvent excipient according to claim 8, wherein said water absorbing radical is a -R-COO^-A^+ radical, wherein R is a lower alkyl group having 1-4 carbon atoms; wherein A^+ is Na^+, or K^+ ~~or Ca^{++}~~.

Claim 11 has been cancelled.

The first claim 21 has been amended as follows:

21. (Amended) The method according to claim 2720, wherein said water absorbing radical is a (-$RCOO^-A^+$) radical, wherein R is a lower alkyl group having 1-4 carbon atoms; wherein A^+ is Na^+, or K^+ ~~or Ca^{++}~~.

The second claim 21 has been cancelled.

Claim 26 has been amended as follows:

Claim 26. (Once Amended) The method according to claim 18, wherein said polysaccharide based material is one selected from the group consisting of potato starch, corn starch, amylose, amylopectin, gelatin, ~~starch 1500,~~ sodium starch glycolate, cellulose, microcrystalline cellulose, hydroxypropyl cellulose, carboxymethyl cellulose, croscarmellose, hydroxypropyl-methyl-cellulose, and chitosan.